

What is claimed is:

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1. A method for determining whether an agent increases brain progenitor cell division comprising: (i) administering the agent to a non-human subject; and (ii). determining whether the resulting brain progenitor cell division in the subject is greater than that in a subject to which the agent was not administered, thereby determining whether the agent increases brain progenitor cell division.
  2. The method of claim 1 comprising the steps of:
    - (a) administering the agent to the subject for a suitable duration of time;
    - (b) administering to the subject a compound which is a marker of cell division;
    - (c) sacrificing the subject after a suitable period of time;
    - (d) quantitatively determining incorporation of the compound in the subject's brain tissue; and
    - (e) comparing the amount so determined with the amount of compound in the brain tissue of a subject to which the agent was not administered,the agent's ability to increase brain progenitor cell division being indicated when the amount of compound in the brain tissue of the subject to which the agent was administered is greater than the amount of compound in the brain tissue of the subject to which the agent was not administered.
  3. The method of claim 2, wherein the subject is a mouse, rat or non-human primate.

4. The method of claim 2, wherein the suitable period of times in step (c) is between 2 and 24 hours.
  5. The method of claim 2, wherein the compound of step (b) is bromodeoxyuridine.
  6. The method of claim 2, wherein the subject's brain tissue in step (d) is hippocampal tissue or subventricular tissue.  
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  7. The method of claim 2, wherein step (d) comprises the steps of: (i) perfusing the tissue with formaldehyde; (ii) sectioning the brain tissue; (iii) staining the tissue sections with anti-BRDU antibody; and (iv) counting the cells labeled with anti-BRDU antibody.  
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  8. The method of claim 1 comprising the steps of:  
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    - (a) administering the agent to the subject for a suitable duration of time;
    - (b) sacrificing the subject after a suitable period of time;
    - (c) determining, *ex vivo*, the amount of protein and/or nucleic acid in the subject's brain tissue indicative of brain progenitor cell division; and  
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    - (d) comparing the amount so determined with the amount of such protein and/or nucleic acid in the brain tissue of a subject to which the agent was not administered, as determined *ex vivo*,  
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- the agent's ability to increase brain progenitor cell division being indicated when the amount of such protein and/or nucleic acid in the brain tissue

of the subject to which the agent was administered is greater than that in the brain tissue of the subject to which the agent was not administered.

5 9. The method of claim 8, wherein the subject is a mouse, rat or non-human primate.

10. The method of claim 8, wherein the subject's brain tissue in step (c) is hippocampal tissue or  
10 subventricular tissue.

11. The method of claim 8, wherein step (c) comprises the steps of: (i) extracting mRNA indicative of progenitor cell division from the brain tissue; and  
15 (ii) using PCR to quantitate the mRNA indicative of progenitor cell division.

12. The method of claim 11, wherein the mRNA is selected from the group consisting of mRNA encoding Ki-67, a cyclin, a nestin, a cyclin-dependant kinase (CDK), and any combination thereof.  
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13. The method of claim 11, wherein step (ii) uses real-time PCR.  
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14. The method of claim 8, wherein step (c) comprises quantitatively determining the amount of protein in the subject's brain tissue by means of immunohistochemistry or Western blot.  
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30 15. The method of claim 1, wherein the agent has no known function.

16. The method of claim 1, wherein the agent is a known therapeutic compound for treating a cognitive disorder.
- 5 17. The method of claim 16, wherein the cognitive disorder is Alzheimer's disease, mild cognitive impairment, multi-infarctual dementia, or schizophrenia.
- 10 18. The method of claim 1, wherein the agent is a known therapeutic compound for treating anxiety, depression, and/or schizophrenia.
- 15 19. The method of claim 1, wherein the agent is a known therapeutic compound for treating a non-mental disorder.
- 20 20. The method of claim 1, wherein the agent is known to stimulate a cellular pathway whose stimulation is associated with an increase in cell division.
- 25 21. The method of claim 1, wherein the agent is known to inhibit a cellular pathway whose inhibition is associated with cell division.
22. The method of claim 1, wherein the agent is known to bind to or otherwise affect a known receptor, transporter, enzyme, or other molecular target.
- 30 23. The method of claim 1, wherein the agent is selected from the group consisting of tricyclics, selective serotonin reuptake inhibitors, selective norepinephrine uptake inhibitors, serotonin norepinephrine uptake inhibitors, alpha-2-adrenergic

antagonists, growth factor receptor activators or modulators, phosphodiesterase inhibitors, NK1 antagonists, vasopressin V1B antagonists, mono-amino oxidase inhibitors, neuroleptics, antipsychotic inhibitors, GSK $\beta$ 3 inhibitors, and agents that upregulate the sonic hedgehog pathway.

24. The method of claim 23, wherein the agent upregulates the sonic hedgehog pathway.

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25. The method of claim 24, wherein the agent is an antagonist of Patched protein in the sonic hedgehog pathway.

15 26. The method of claim 24, wherein the agent is an agonist of Smoothened protein in the sonic hedgehog pathway.

20 27. The method of claim 24, wherein the agent is selected from the group consisting of Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3.

25 28. A method for treating anxiety, depression, a cognitive disorder or a neuro-degenerative disorder by administering to an afflicted subject a therapeutically effective amount of an agent determined to have the ability to increase brain progenitor cell division, wherein such ability is determined by a method comprising (i) administering the agent to a non-human subject, and (ii) determining whether the resulting brain progenitor cell division in the subject is greater than that in a subject to which the agent was not administered.

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29. The method of claim 28, wherein the agent is selected from the group consisting of trycyclics, selective serotonin reuptake inhibitors, selective norepinephrine uptake inhibitors, serotonin norepinephrine uptake inhibitors, alpha-2-adrenergic antagonists, growth factor receptor activators or modulators, phosphodiesterase inhibitors, NK1 antagonists, vasopressin V1B antagonists, mono-amino oxidase inhibitors, neuroleptics, antipsychotic inhibitors, GSK-3 beta inhibitors, and agents that upregulate the sonic hedgehog pathway.
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30. The method of claim 29, wherein the agent upregulates the sonic hedgehog pathway.
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31. The method of claim 30, wherein the agent is an antagonist of Patched protein in the sonic hedgehog pathway.
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32. The method of claim 30, wherein the agent is an agonist of Smoothened protein in the sonic hedgehog pathway.
33. The method of claim 30, wherein the agent is selected from the group consisting of Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3.
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34. The method of claim 28, wherein the subject is a human.
35. A method for inhibiting the onset of anxiety, depression or a cognitive disorder by administering

to a subject in need thereof a prophylactically effective amount of an agent determined as having the ability to increase brain progenitor cell division, wherein such ability is determined by a method comprising (i) administering the agent to a non-human subject, and (ii) determining whether the resulting brain progenitor cell division in the subject is greater than that in a subject to which the agent was not administered.

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36. The method of claim 35, wherein the agent is selected from the group consisting of tricyclics, selective serotonin reuptake inhibitors, NK1 antagonists, vasopressin V1B antagonists, mono-amino oxidase inhibitors, neuroleptics, antipsychotic inhibitors, GSK $\beta$ 3 inhibitors, and agents that upregulate the sonic hedgehog pathway.

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37. The method of claim 36, wherein the agent upregulates the sonic hedgehog pathway.

38. The method of claim 37, wherein the agent is an antagonist of Patched protein in the sonic hedgehog pathway.

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39. The method of claim 37, wherein the agent is an agonist of Smoothened protein in the sonic hedgehog pathway.

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40. The method of claim 37, wherein the agent is selected from the group consisting of Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3.

41. The method of claim 35, wherein the subject is a human.
42. A composition comprising (a) a pharmaceutically acceptable carrier, and (b) an agent determined as having the ability to increase brain progenitor cell division, wherein such ability is determined by a method comprising (i) administering the agent to a non-human subject, and (ii) determining whether the resulting brain progenitor cell division in the subject is greater than that in a subject to which the agent was not administered.  
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43. The method of claim 42, wherein the agent is selected from the group consisting of trycyclics, selective serotonin reuptake inhibitors, selective norepinephrine uptake inhibitors, serotonin norepinephrine uptake inhibitors, alpha-2-adrenergic antagonists, growth factor receptor activators or modulators, phosphodiesterase inhibitors, NK1 antagonists, vasopressin V1B antagonists, mono-amino oxidase inhibitors, neuroleptics, antipsychotic inhibitors, GSK-3 beta inhibitors, and agents that upregulate the sonic hedgehog pathway.  
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44. The composition of claim 42, wherein the agent upregulates the sonic hedgehog pathway.
45. The composition of claim 44, wherein the agent is an antagonist of Patched protein in the sonic hedgehog pathway.  
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46. The composition of claim 44, wherein the agent is an agonist of Smoothened protein in the sonic hedgehog pathway.
- 5 47. The composition of claim 44, wherein the agent is selected from the group consisting of Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3.
- 10 48. An article of manufacture comprising a packaging material having therein an agent determined as having the ability to increase brain progenitor cell division, and a label indicating a use of the agent for inhibiting the onset of anxiety, depression, a cognitive disorder or a neurodegenerative disorder in a subject, wherein such ability is determined by a method comprising (i) administering the agent to a non-human subject, and (ii) determining whether the resulting brain progenitor cell division in the subject is greater than that in a subject to which the agent was not administered.
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49. The article of claim 48, wherein the agent is selected from the group consisting of trycyclics, selective serotonin reuptake inhibitors, selective norepinephrine uptake inhibitors, serotonin norepinephrine uptake inhibitors, alpha-2-adrenergic antagonists, growth factor receptor activators or modulators, phosphodiesterase inhibitors, NK1 antagonists, vasopressin V1B antagonists, mono-amino oxidase inhibitors, neuroleptics, antipsychotic inhibitors, GSK $\beta$ 3 inhibitors, and agents that upregulate the sonic hedgehog pathway.

50. The article of claim 49, wherein the agent upregulates the sonic hedgehog pathway.
51. The article of claim 50, wherein the agent is an antagonist of Patched protein in the sonic hedgehog pathway.  
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52. The article of claim 50, wherein the agent is an agonist of Smoothened protein in the sonic hedgehog pathway.  
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53. The article of claim 50, wherein the agent is selected from the group consisting of Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3.  
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54. The article of claim 48, wherein the subject is a human.
- 20 55. An article of manufacture comprising a packaging material having therein an agent determined as having the ability to increase brain progenitor cell division, and a label indicating a use of the agent for treating anxiety, depression, a cognitive disorder or a neurodegenerative disorder in a subject, wherein such ability is determined by a method comprising (i) administering the agent to a non-human subject, and (ii) determining whether the resulting brain progenitor cell division in the subject is greater than that in a subject to which the agent was not administered.  
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56. The article of claim 55, wherein the agent is selected from the group consisting of trycyclics,

selective serotonin reuptake inhibitors, NK1 antagonists, vasopressin V1B antagonists, mono-amino oxidase inhibitors, neuroleptics, antipsychotic inhibitors, GSK $\beta$ 3 inhibitors, and agents that upregulate the sonic hedgehog pathway.

- 5 57. The article of claim 56, wherein the agent upregulates the sonic hedgehog pathway.
- 10 58. The article of claim 57, wherein the agent is an antagonist of Patched protein in the sonic hedgehog pathway.
- 15 59. The article of claim 57, wherein the agent is an agonist of Smoothened protein in the sonic hedgehog pathway.
- 20 60. The article of claim 57, wherein the agent is selected from the group consisting of Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3.
- 25 61. The article of claim 55, wherein the subject is a human.
- 30 62. A method for treating anxiety, depression, a cognitive disorder or a neuro-degenerative disorder by administering to an afflicted subject a therapeutically effective amount of Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3.
63. A method for inhibiting the onset of anxiety, depression or a cognitive disorder by administering

to a subject in need thereof a prophylactically effective amount of Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3.

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64. A composition comprising (a) a pharmaceutically acceptable carrier, and (b) Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3.

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65. An article of manufacture comprising a packaging material having therein Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3 and a label indicating a use of Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3 for inhibiting the onset of anxiety, depression or a cognitive disorder in a subject.

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66. An article of manufacture comprising a packaging material having therein Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3 and a label indicating a use of Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, or a derivative of Hh-Ag 1.1, Hh-Ag 1.2 or Hh-Ag 1.3 for treating anxiety, depression, a cognitive disorder or a neurodegenerative disorder in a subject.

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